(12) UK Patent Application (19) GB (11) 2 287 706 (13) A

(43) Date of A Publication 27.09.1995

(21) Application No 9405533.2

(22) Date of Filing 21.03.1994

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(51) INT CL^6
C07D 471/04 , A61K 31/44

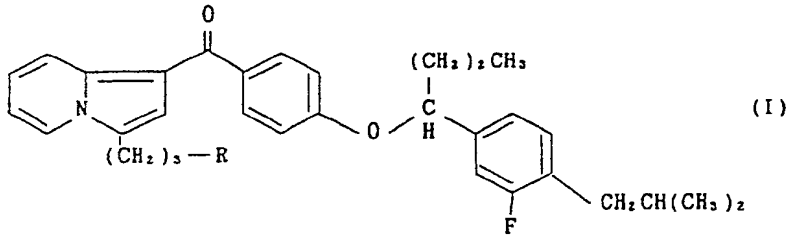
(52) UK CL (Edition N)
C2C CAA CMM CQU CTX CUK C1173 C1352 C1492 C200 C202 C214 C215 C22Y C220 C225 C226 C25Y C250 C251 C253 C28X C29X C29Y C292 C31Y C311 C313 C315 C332 C338 C339 C35X C351 C352 C355 C36Y C364 C365 C366 C367 C368 C389 C396 C463 C464 C490 C50Y C500 C612 C621 C623 C624 C625 C628 C634 C635 C638 C644 C65X C658 C659 C66X C661 C662 C665 C675 C681 C697 C699 C761 C769 C771 C802
U1S S2416

(56) Documents Cited
None

(58) Field of Search
UK CL (Edition N) C2C CUK
INT CL^6 C07D
Online: CAS.

(54) **Indolizine derivatives**

(57) A compound of the formula (I) :



(I)

wherein R is a carboxy of protected carboxy, or a pharmaceutically acceptable salt thereof. The compound of the present invention is useful as a testosterone 5α -reductase inhibitor and effective for testosterone 5α -reductase-mediated diseases such as prostatism, prostatic hypertrophy, prostatic cancer, alopecia, hirsutism (e.g. female hirsutism), androgenic alopecia (or male-pattern baldness), acne (e.g. acne vulgaris, pimple), other hyperandrogenisms, and the like.

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AL

HETEROCYCLIC DERIVATIVES

The present invention relates to novel heterocyclic derivatives and pharmaceutically acceptable salts thereof. More particularly, it relates to novel heterocyclic derivatives and pharmaceutically acceptable salts thereof, which have pharmacological activities such as inhibitory activity on testosterone 5α-reductase, to a process for the preparation thereof, to a pharmaceutical composition containing the same, and to a use of the same as a medicament.

It has hitherto been known that heterocyclic derivatives are effective for testosterone 5α-reductase-mediated diseases. However, a testosterone 5α-reductase inhibitor with stronger effects has been demended.

Accordingly, one object of the present invention is to provide novel heterocyclic derivatives and pharmaceutically acceptable salts thereof, which are useful as a testosterone 5α-reductase inhibitor.

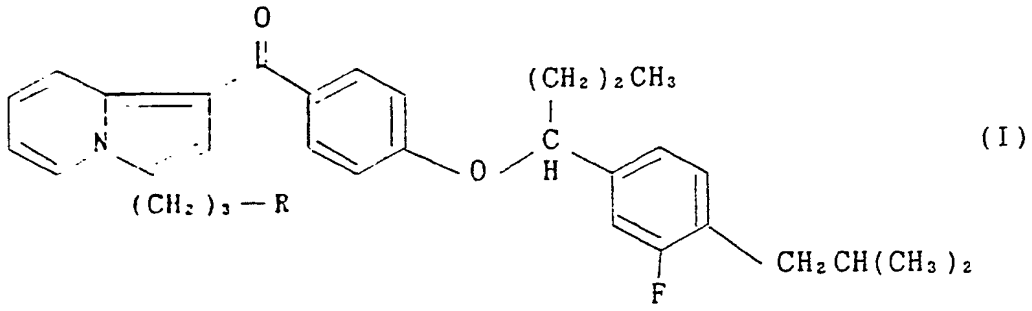
Another object of the present invention is to provide a process for the preparation of said heterocyclic derivatives or salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said heterocyclic derivative or a pharmaceutically acceptable salt thereof.

A still further object of the present invention is to

provide use of said heterocyclic derivatives or pharmaceutically acceptable salts thereof as a medicament such as a testosterone 5α-reductase inhibitor useful for treating or preventing testosterone 5α-reductase-mediated diseases such as alopecia, acnes and prostatism in human being or animals.

Heterocyclic derivatives of the present invention are novel and can be represented by the formula (I):

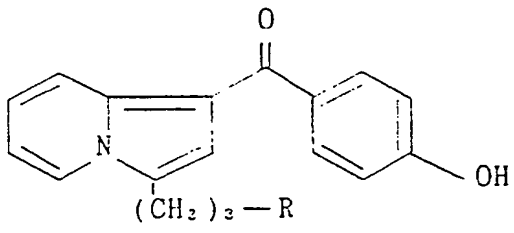


(I)

wherein R is a carboxy group or protected carboxy.

According to the present invention, the object compound (I) and a salt thereof can be prepared by the following processes.

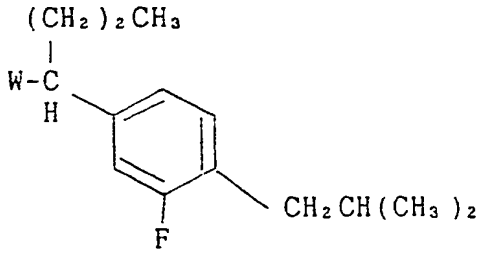
Process 1



(II)

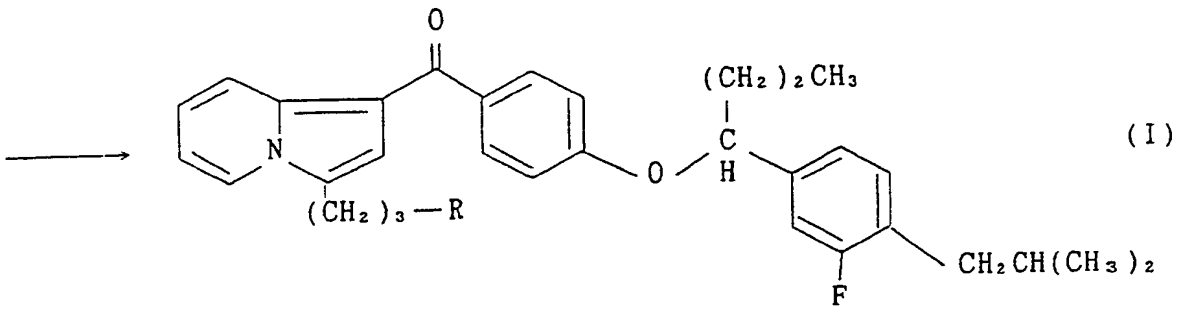
or a salt thereof

+



(III)

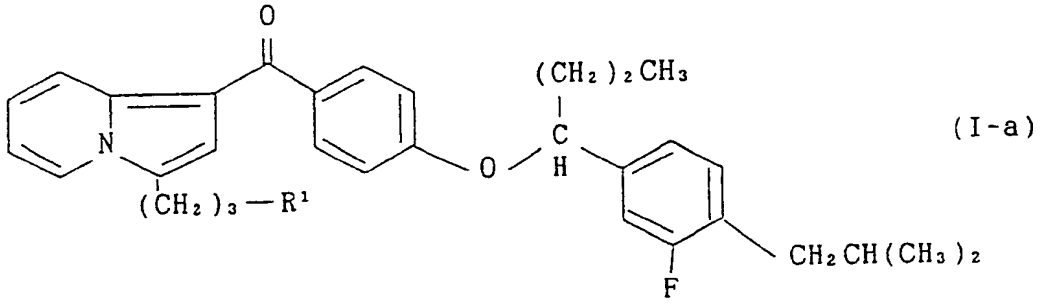
or a salt thereof



(I)

or a salt thereof

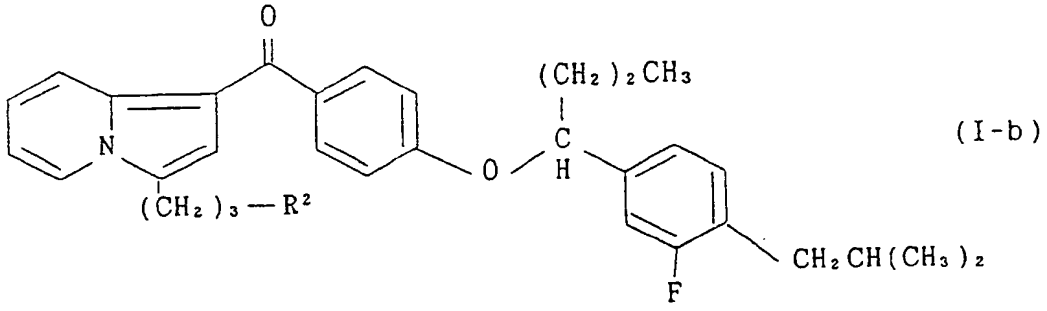
Process 2



(I-a)

or a salt thereof

Elimination of the carboxy-protective group



(I-b)

or a salt thereof

wherein R is as defined above,

R^1 is a protected carboxy,

R^2 is a carboxy group, and

W is a leavig group.

Suitable salts of the compound (I) are conventional, non-toxic, pharmaceutically acceptable salts, and include salts with base or acid addition salts. There are exemplified salts with inorganic bases such as alkali metal salts (e.g. sodium salt, potassium salt, cesium salt), alkaline earth metal salts (e.g. calcium salt, magnesium salt) and ammonium salts; salts with organic bases such as organic amine salts (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt); inorganic acid addition salts (e.g. hydrochloride, hydrobromide, sulfate, phosphate); organic carboxylic or sulfonic acid addition salts (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate); and salts with basic or acidic amino acids (e.g. arginine, aspartic acid, glutamic acid). The preferable salts are acid addition salts.

Suitable examples of the salts of the compounds (I-a), (I-b), (II) and (III) in Processes 1 and 2 are to be referred to those as exemplified for the object compound (I).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are detailedly as follows:

Suitable "protected carboxy" includes commonly protected

carboxy such as esterified carboxy groups.

Suitable examples of the ester moiety of "esterified carboxy" include, for instance, lower alkyl esters (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester) which may have one or more suitable substituents such as lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyl-oxyethyl ester], lower alkanesulfonyl(lower)alkyl ester [e.g. 2-mesylethyl ester], mono(or di or tri)-halo(lower)alkyl ester [e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester], lower alkoxycarbonyloxy(lower)alkyl ester [e.g. methoxycarbonyloxy-methyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyl-oxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxy-carbonyloxyethyl ester], phthalidylidene(lower)alkyl ester, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)-ethyl ester]; lower alkenyl ester [e.g. vinyl ester, allyl

ester]; lower alkynyl esters [e.g. ethynyl ester, propynyl ester]; ar(lower)alkyl esters which may have one or more suitable substituents [e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester]; aryl esters which may have one or more suitable substituents [e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester]; and phthalidyl ester.

Preferable examples of the esterified carboxy as mentioned above include lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, 1-cyclopropylethoxycarbonyl).

The term "lower" means that the number of carbon atom is from 1 to 6, preferably 1 to 4, unless otherwise indicated.

Suitable "leaving group" includes hydroxy, and reactive groups derived from hydroxy.

Suitable "reactive group derived from hydroxy" includes acid residues.

Suitable "acid residue" includes halogen (e.g. fluoro, chloro, bromo, iodo) and acyloxy (e.g. acetoxy, tosyloxy, mesyloxy).

The processes 1 and 2 for preparing the object compound (I)

of the present invention are explained in detail in the following.

Process 1

The object compound (I) and a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salts of the compounds (II) and (III) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in a solvent such as an alcohol [e.g. methanol, ethanol], dichloromethane, benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether, toluene or any other solvent which does not adversely affect the reaction. These solvents may be used alone or upon mixing with one another.

In this reaction, when W in the compound (III) is an acid residue, the reaction may be carried out in the presence of an inorganic or organic base. Examples of the base are alkali metal hydroxides [e.g. sodium hydroxide, potassium hydroxide], alkali metal carbonates [e.g. sodium carbonate, potassium carbonate], alkali metal bicarbonates [e.g. sodium bicarbonate, potassium bicarbonate], alkali metal hydrides [e.g. sodium hydride, potassium hydride], tri(lower)alkylamines [e.g. trimethylamine, triethylamine, diisopropylethylamine], and pyridine and its derivatives [e.g. picoline, lutidine, 4-dimethylaminopyridine]. In case where the base to be used is a liquid, it can also be used as a solvent.

When W in the compound (III) is hydroxy, this reaction is usually carried out in the presence of a conventional condensing agent. Examples of the condensing agent are N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate]; a combination of triarylphosphine [e.g. triphenylphosphine] or tri(lower)alkylphosphine [e.g. triethylphosphine], and di(lower)alkyl azodicarboxylate [e.g. diethyl azodicarboxylate]; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride; phosgene; trichloromethyl chloroformate; and phosphorus oxychloride.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at room temperature or under warming or heating.

Precess 2

The object compound (I-b) and a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to an elimination reaction of the carboxy-protective group.

In the present elimination reaction, all conventional methods used for the elimination of the carboxy-protective group, for example, hydrolysis, reduction, elimination using a Lewis acid, etc. are applicable. When the carboxy-protective group is an ester, it can be eliminated by hydrolysis or elimination using a Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base includes, for example, inorganic bases such as alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (e.g. magnesium hydroxide, calcium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), alkaline earth metal carbonates (e.g. magnesium carbonate, calcium carbonate), alkali metal bicarbonates (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal acetates (e.g. sodium acetate, potassium acetate), alkali earth metal phosphates (e.g. magnesium phosphate, calcium phosphate), and alkali metal hydrogen phosphates (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate); and organic bases such as trialkylamines (e.g. trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, and 1,5-diazabicyclo-[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, and 1,5-diazabicyclo[5.4.0]undecene-5. The hydrolysis using a base is

often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid includes organic acids (e.g. formic acid, acetic acid, propionic acid) and inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid). The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and it may be selected suitably in accordance with the kind of carboxy protective group and elimination method to be employed.

The elimination using a Lewis acid is preferable for eliminating a substituted or unsubstituted ar(lower)alkyl ester, and carried out by reacting the compound (I-a) or a salt thereof with a Lewis acid. Examples of the Lewis acid are boron trihalides (e.g. boron trichloride, boron trifluoride), titanium tetrahalides (e.g. titanium tetrachloride, titanium tetrabromide), tin tetrahalides (e.g. tin tetrachloride, tin tetrabromide), aluminum halides (e.g. aluminum chloride, aluminum bromide), and trihaloacetic acids (e.g. trichloroacetic acid, trifluoroacetic acid). This elimination reaction is preferably carried out in the presence of a cation trapping agent (e.g. anisole, phenol) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane), alkylene halide (e.g. methylene chloride, ethylene chloride), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction.

These solvents may be used alone or upon mixing with one another.

A reduction elimination can be preferably conducted for eliminating protective group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl) ester, and ar(lower)alkyl (e.g. benzyl) ester.

The reduction applicable for the elimination reaction includes the reduction using a combination of a metal (e.g. zinc, zinc amalgam) or a salt of chromium compound (e.g. chromous chloride, chromous acetate) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid); and a conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel).

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

The starting compound (II) include novel compounds which can be prepared by the following method or in a conventional manner.

The object compound (I) of the present invention can be isolated and purified in a conventional manner such as extraction, precipitation, fractional crystallization, recrystallization, or chromatography.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The object compound (I) of the present invention is useful as a testosterone 5 α-reductase inhibitor and effective for testosterone 5α-reductase-mediated diseases such as prostatism, prostatic hypertrophy, prostatic cancer, alopecia, hirsutism (e.g. female hirsutism), androgenic alopecia (or male-pattern baldness), acne (e.g. acne vulgaris, pimple), other hyperandrogenism, and the like.

For therapeutic or preventive administration, the object compound (I) of the present invention is used in the form of a conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable, substantially non-toxic carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparation may be in a solid form such as tablet, granule, powder or capsule, or a liquid form such as solution, suspension, syrup, emulsion, lemonade or lotion.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly-used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, and ethylene glycol.

While the dosage of the compound (I) may vary depending upon age and conditions of patients, the kind of diseases or conditions, the kind of the compound (I) to be used, etc. In

general, amounts between about 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used for treating diseases.

The following Example is given for the purpose of illustrating the present invention.

Example

[Step 1] : Diethyl azodicarboxylate (0.139 ml) was added to a mixture of ethyl 4-[1-(4-hydroxybenzoyl)-3-indolizinyl]-butyrate (281 mg), (R)-1-(3-fluoro-4-isobutylphenyl)butanol (179 mg) and triphenylphosphine (231 mg) in a mixture of tetrahydrofuran (1.5 ml) and toluene (6 ml) at -20℃. The mixture was stirred at -20℃ for 5 hours, and then acetic acid (2 drops) was added. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (a mixture of hexane and ethyl acetate = 3 : 1 by volume as eluent) to give ethyl 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)butyloxy]benzoyl]-3-indolizinyl]butyrate as an oil.

^{1}H-NMR (200 MHz, $CDCl_3$, δ) : 0.8 - 1.0 (m, 9H), 1.2 - 1.65 (m, 5H), 1.7 - 2.2 (m, 5H), 2.44 (m, 4H), 2.88 (t, 2H, J=7Hz), 4.12 (q, 2H, J=7Hz), 5.17 (dd, 1H, J=5Hz, 8Hz), 6.8 - 7.2 (m, 8H), 7.75 (d, 2H, J=9Hz), 7.98 (d, 1H, J=7Hz), 8.44 (d, 1H, 9Hz)

[Step 2] : To a solution of ethyl 4-[1-[4-(S)-[1-(3-fluoro-

4-isobutylphenyl)butyloxy]benzoyl]-3-indolizinyl]butyrate (236 mg) in ethanol (3 ml) and 1,4-dioxane (3 ml) was added 1N sodium hydroxide (1.5 ml). The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated, diluted hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and concentrated to give 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)butyloxy]benzoyl]-3-indolizinyl]butyric acid (194 mg) as powder.

^{1}H-NMR (200 MHz, $CDCl_3$, δ) : 0.85 - 1.05 (m, 9H), 1.3 - 1.65 (m, 2H), 1.7 - 2.2 (m, 5H), 2.49 (m, 4H), 2.90 (t, 2H, J=7Hz), 5.15 (dd, 1H, J=5Hz, 8Hz), 6.8 - 7.2 (m, 8H), 7.73 (d, 2H, J=9Hz), 7.96 (d, 1H, J=7Hz), 8.44 (d, 1H, J=9Hz)

Reference Example

[Step 1] The procedure of Example, Step 1 was repeated except that (R)-1-(3-fluoro-4-isobutylphenyl)pentanol was used in place of (R)-1-(3-fluoro-4-isobutylphenyl)butanol to give ethyl 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)pentyloxy]-benzoyl]-3-indolizinyl]butyrate was obtained.

^{1}H-NMR (200 MHz, $CDCl_3$, δ) : 0.92 (m, 9H), 1.2 - 1.6 (m, 7H), 1.75 - 2.15 (m, 5H), 2.45 (m, 4H), 2.88 (t, 2H, J=7Hz), 4.12 (q, 2H, J=7Hz), 5.14 (dd, 1H, J=5Hz, 8Hz), 6.8 - 7.2 (m, 8H), 7.75 (d, 2H, J=9Hz), 7.98 (d, 1H, J=7Hz), 8.45 (d, 1H, 9Hz)

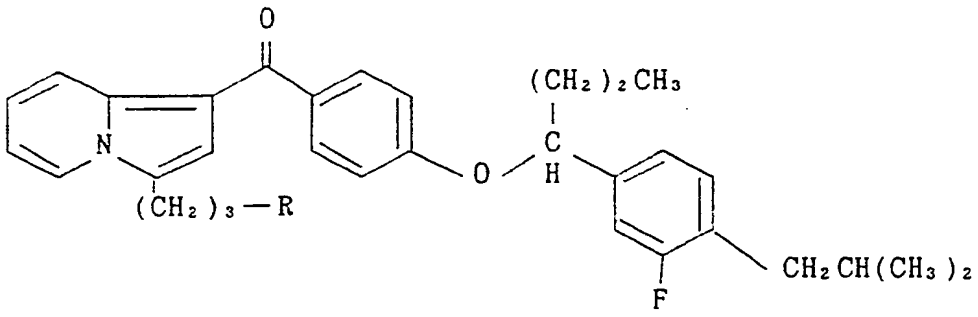
[Step 2] The procedure of Example, Step 2 was repeated

except that ethyl 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)-pentyloxy]benzoyl]-3-indolizinyl]butyrate was used in place of ethyl 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)butyloxy]-benzoyl]-3-indolizinyl]butyrate to give 4-[1-[4-(S)-[1-(3-fluoro-4-isobutylphenyl)pentyloxy]benzoyl]-3-indolizinyl]-butyric acid.

^{1}H-NMR (200 MHz, $CDCl_3$, δ) : 0.90 (m, 9H), 1.3 - 1.6 (m, 4H), 1.7 - 2.2 (m, 5H), 2.49 (m, 4H), 2.90 (t, 2H, J=7Hz), 5.13 (dd, 1H, J=5Hz, 8Hz), 6.8 - 7.2 (m, 8H), 7.74 (d, 2H, J=9Hz), 7.95 (d, 1H, J=7Hz), 8.43 (d, 1H, 9Hz)

What we claim is :

1. A compound of the formula (I) :

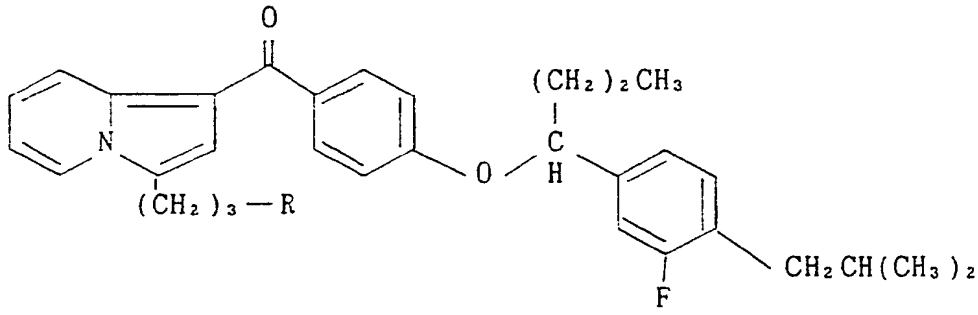


(I)

wherein R is a carboxy group or protected carboxy,

or a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of the formula (I):



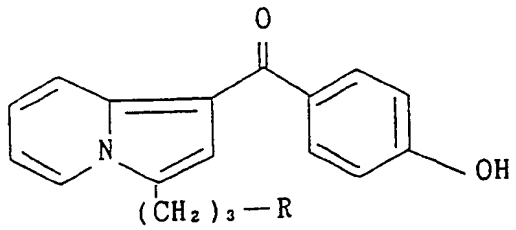
(I)

wherein R is a carboxy group or protected carboxy,

or a pharmaceutically acceptable salt thereof,

which comprises:

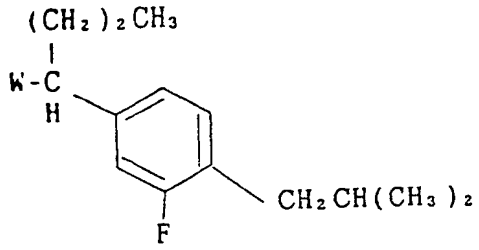
(1) reacting a compound of the formula (II):



(II)

wherein R is as defined above,

or a salt thereof, with a compound of the formula (III) :

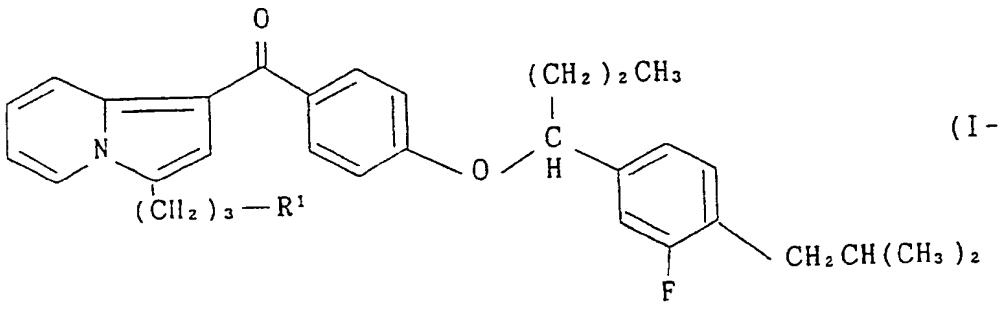


(III)

wherein W is a leaving group,

or a salt thereof; or

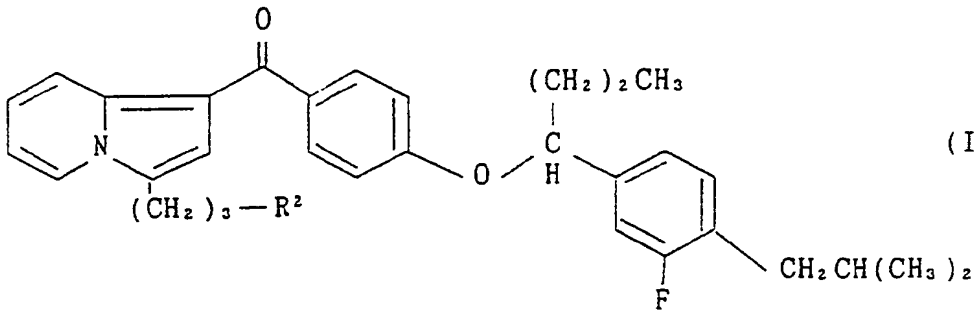
(2) subjecting a compound of the formula (I-a) :



(I-a)

wherein R^1 is a protected carboxy,

or a salt thereof, to an elimination reaction of the carboxy-protective group to give a compound of the formula (I-b) :



(I-b)

wherein R^2 is a carboxy, or a salt thereof.

3. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof in association with pharmaceutically acceptable carriers or excipients.

4. A method for treating or preventing testosterone 5α-reductase-mediated diseases, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

5. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

6. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a testosterone 5α-reductase inhibitor.

7. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically

acceptable salt thereof with pharmaceutically acceptable carriers or excipients.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9405533.2

Relevant Technical Fields

(i) UK Cl (Ed.N) C2C (CUK)

(ii) Int Cl (Ed.6) C07D

Search Examiner
MR R HONEYWOOD

Date of completion of Search
18 MAY 1995

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE: CAS

Documents considered relevant following a search in respect of Claims :-
1-7

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
	NONE	

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).